REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Summary of Telephonic Interview

Applicants wish to thank the Examiner for participating in the telephonic interview with Applicants' representative on November 17, 2009. During the interview, the rejections of record were discussed, as well as Applicants' proposed amendments and arguments.

The Examiner indicated that the proposed amendments to claim 1, (as submitted in this response), as well as the new evidence (submitted herewith as New Table 2) should overcome the three prior art rejections.

Additionally, regarding the enablement rejection, the Examiner has requested that Applicants again set forth their arguments regarding this rejection. The Examiner appeared to indicate that, in view of the amendments and arguments of record, this rejection would likely be withdrawn.

Applicants submit herewith the proposed amendments, arguments and evidence discussed during the personal interview, and appreciate the Examiner's helpful comments.

Claim Amendments

Claim 1 has been amended to delete the monocyclic heteroaryl groups from the aromatic ring groups which are listed for Ar in formula (I), and to delete substituted or unsubstituted phenyl from the definition of X^1.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 18-22 and 25 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner states that while enabling for pyrimidine derivatives of formula (I) in which ring A is saturated, unsaturated or partially saturated carbohexyl group, X^1 is amino or methyl, X^2 is hydrogen, Y is a direct bond, n is 3, and Ar is the group represented by the second formula listed, the specification does not enable the instant compounds to treat IBS with compounds of any other permutation of formula (I).

Applicants respectfully disagree with the Examiner's position.

Regarding claims 18 and 19, the compounds recited in these claims have been previously restricted to those for which pharmacological data is provided in the specification. Specifically, Tables A-1 and A-2 on pages 48-51 of the specification show the affinity of the recited compounds of 5-HT_{1A} and 5-HT_3 receptors. Tables B-1 and B-2 on page 52 of the specification show in vivo 5-HT_{1A} agonistic activity of the compounds. Tables C-1 and C-2 on pages 53-54 of the specification show in vivo 5-HT_3 antagonistic activity, and Table D on page 56 shows the action of the compounds on defecation under stress.

Although Tables B-1, B-2, C-1, C-2 and D do not provide data for each of the recited compounds, these tables provide data for a representative number of compounds. Applicants are not required to provide data for each claimed compound, but rather are permitted to provide a representative sampling of the compounds. Additionally, Tables A-1 and A-2 provide pharmacological data demonstrating that each of the recited compounds demonstrate affinity to 5-HT_{1A} and 5-HT_3 receptors. Applicants have discovered (as discussed in the paragraph spanning pages 2 and 3 of the specification) that simultaneous expression in vivo of 5-HT_3 antagonistic activity and 5-HT_{1A} agonistic activity is very effective for treating the diseases associated with both hyperactivity or expression enhancement of 5-HT_3 and hypoactivity of 5-HT_{1A}, in particular, IBS.

Since compounds having particular activity are concretely discussed in the specification, together with their pharmacological data, one of ordinary skill in the art would have been able to make and use the invention, based upon the teachings of the specification, without undue experimentation.

Claim 20 recites a limited number of compounds from the compounds which are recited in claim 19. Accordingly, the subject matter of claim 20 is also enabled by the specification for the same reasons discussed above.

Claims 21 and 22 have already been restricted to particular 5-HT_3 antagonistic agents, and the 5-HT_{1A} agonistic agent has been restricted to tandospirone. These compounds are widely known to have 5-HT_{1A} agonistic activity and 5-HT_3 antagonistic activity. Accordingly, Applicants respectfully assert that these claims are enabled by the specification, in view of the knowledge of one of ordinary skill in the art.

Lastly, claim 25 is enabled for the same reasons discussed above regarding claims 19 and 20.

Accordingly, it is evident that Applicants' claims are enabled by the specification, and it is respectfully requested that the above-rejection should be withdrawn.

Consideration After Final Rejection

Although this Amendment is presented after final rejection, the Examiner is respectfully requested to enter the amendments and consider the remarks, as they place the application in condition for allowance.

Patentability Arguments

The patentability of the present invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Rejection Under 35 U.S.C. § 102(b)

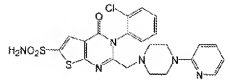
Claims 1, 9, 10 and 15 are rejected under 35 U.S.C. § 102(b) as being anticipated by Arita et al. (EP 0 364 598).

The Examiner takes the position that Example No. 41 of Arita et al. anticipates Applicants' claims, where X^1 is phenyl substituted with chloro, A is a heterocyclic group substituted with SO_2NH_2, Y is a direct bond, n is 0, X^2 is hydrogen, and Ar is the first choice (pyridine).

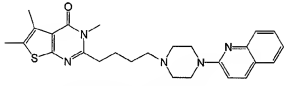
This rejection is respectfully traversed.

Arita et al. disclose compounds wherein the 3-position of 3,4-dihydrothieno[2,3-d]pyrimidine is directly substituted with a phenyl group. However, Applicants have amended the claims to delete "substituted or unsubstituted phenyl" from the definition of X^1 of formula (I).

Additionally, the Examiner says, "The closest example to Example No. 41 of the reference (EP 0 364 598) is Example 23 found on instant page 162." The structures of the compounds of these two Examples are as follows:



Example No. 41 in EP364598



Example 7-23 in this invention

Although the Examiner compares the two compounds with each other, as demonstrated by the structures shown above, these compounds are structurally quite different from each other.

In view of the reasons set forth above, it is evident that the subject matter of Applicants' claims is patentable over the disclosure of Arita et al. It is respectfully requested that the above-rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 1, 6, 8-11 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Modica et al. (Arylpiperazinyl…, J. Med. Chem. 40 (1997)).

[Applicants note that the second paragraph of this rejection refers to Ashkinazi et al., rather than Modica et al. Applicants presume this was an inadvertent error, and Applicants refer only to Modica et al. in the following remarks.]

The Examiner takes the position that Modica et al. teach a compound which renders Applicants' compound obvious, where X^1 is amino or methyl, A is a heterocyclic group di-substituted with methyl, Y is sulfur, n is 2, X^2 is hydrogen and Ar is pyrimidine.

This rejection is respectfully traversed.

As discussed above, Applicants have amended the claims to delete the monocyclic heteroaryl groups from the definition of Ar in formula (I). Accordingly, the disclosure relied

upon by the Examiner is no longer appropriate for rejecting Applicants' claims. Thus, it is respectfully requested that this rejection be withdrawn.

Claims 1, 2, 9-11, 13 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Matsuoka et al. (Canada Patent No. 2431406).

The Examiner has maintained this rejection from the previous Office Action. In response to Applicants' previously presented arguments, the Examiner states, "Applicant has provided comparable compounds and argues that the instant compounds provide superior results over the compounds of the reference. Examiner disputes the validity of this comparison as Table 2 shows that the dose of TZB41044 was three times that of the three compared compounds without any explanation from Applicant as to this deviation in standard chemical comparison. Even if this major dosage discrepancy is overlooked by a fact finder the actual numerical variation between LLR, FBP, and BT are not that great between TZB41044 and the three compared compounds."

Applicants agree with the Examiner's statement that "the dose of TZB41044 was three times that of the three compared compounds without any explanation from Applicant". Accordingly, Applicants have prepared and attach hereto a New Table 2, which demonstrates the values of activity of TZB41044 and three compared compounds at various dosages.

In the column of "rat: in vivo agonistic activity" in the attached New Table 2, 10mg/Kg is a common dosage among the four compounds. When the four compounds are compared in activity with one another at this dosage of 10mg/Kg, it is found that the compound wherein the nitrogen atom at the 3-position of pyrimidine ring is unsubstituted (TZB-41044) shows a weak 5-HT_{1A} agonistic activity. Furthermore, at the dosage of 10mg/Kg, TZB-41044 did not lower BT at all.

Since the maximum values of LLR and FBP are 3.0, it can be said that the first three compounds are considerably different in the values of LLR and FBP from the last compound (TZB-41044) in the attached New Table 2.

As for CFS, no data is available at a dosage which is in common with these four compounds (10mg/Kg). However, since TZB-41044 exhibits no anti-anxiety effects at a dosage of 30mg/Kg, it is presumed that TZB-41044 would exhibit no anti-anxiety effects at a smaller dosage (of 10mg/Kg).

Although the previously submitted Table 2 showed the activity of TZB-41044 at a dosage three times that of the other three compounds, this was intended to demonstrate that TZB-41044 has low activity in spite of a large dosage.

However, in view of the Examiner's position discussed above, the attached New Table 2 shows values at one and the same dosage for the compounds compared, except for anti-anxiety effects of TZB-41044; no assay was conducted at a dosage smaller than 30mg/Kg.

It is evident from the results of the attached New Table 2 that the compound wherein the nitrogen atom at the 3-position of pyrimidine ring is unsubstituted (i.e., wherein X^1 = H in formula (I) of the present invention; TZB-41044) shows a weak 5-HT_{1A} agonistic ativity. Accordingly, it is evident that, in 5-HT_{1A} agonistic activity, the above-mentioned compound (with an unsubstituted nitrogen atom at the 3-position of the pyrimidine ring) is clearly distinguished from the compounds of the present invention, wherein the nitrogen atom at the 3-position of the pyrimidine ring is substituted with amino or methyl group.

Furthermore, the monocyclic heteroaryl groups have been deleted from the aromatic ring groups defined as Ar in formula (I). When R_1 denotes a group of piperazine-Ar type in the compounds disclosed in Matsuoka et al., Ar is always a monocyclic heteroaryl. Accordingly, the deletion of monocyclic heteroaryl groups from Ar of the compounds of formula (I) of Applicants' claims further distinguishes the claims from the disclosure of the cited reference.

Matsuoka et al. fail to teach or suggest that, for the treatment of IBS, it is effective to exert 5-HT_{1A} agonistic action and 5-HT_3 antagonistic action in cooperation. Furthermore, Matsuoka et al. fail to disclose any compound which has both 5-HT_{1A} agonistic action and 5-HT_3 antagonistic action, and is thus effective against IBS. Additionally, Applicants have now clearly demonstrated that substitution on the 3-position of the pyrimidine ring results in unexpected advantages, and thus is unobvious from the teachings of Matsuoka et al.

For the reasons set forth in detail above, it is evident that the subject matter of Applicants' claims is patentable over the cited reference. Thus, it is respectfully requested that the above-discussed rejection be withdrawn.

Claim Objection

Claims 3-5, 12, 14, 16, 23 and 24 are objected to as being dependent upon a rejected independent claim, but indicated as allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims. In view of the amendments, arguments and evidence discussed above, Applicants respectfully assert that the claims upon which the objected claims depend are now in condition for allowance. Thus, the objection to the claims should be withdrawn.

Conclusion

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of objection and rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

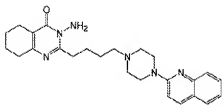
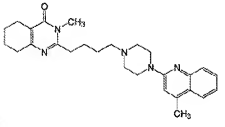
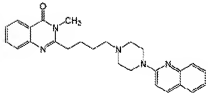
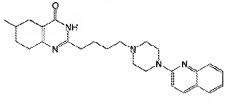
Michitaka SATO et al.

/Amy E. Schmid/
2009.12.07 15:01:01 -05'00'

By _____
Amy E. Schmid
Registration No. 55,965
Attorney for Applicants

AES/a/emj
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
December 7, 2009

New Table 2

Compound Structure	5-HT$_{1A}$ Agonistic Activity			
	rat : in vivo agonistic activity		mouse : anti-anxiety	
	dose (mg/Kg)	score	dose (mg/Kg)	effect
Example 4-1 	3 (i.p.)	LLR:0.0 FBP:0.0 BT*1:-0.3	1 (i.p.)	- (CFS*2)
	10 (i.p.)	LLR:1.5 FBP:1.8 BT*1:-1.4	3 (i.p.)	+ (CFS)
	30 (i.p.)	LLR:2.5 FBP:3.0 BT*1:-3.0	6 (i.p.)	+ (CFS)
Example 7-6 	1 (i.p.)	LLR:0.4 FBP:0.2 BT:-0.1	1 (i.p.)	+ (CFS)
	3 (i.p.)	LLR:1.4 FBP:1.0 BT:-0.9	3 (i.p.)	+ (CFS)
	10 (i.p.)	LLR:2.4 FBP:2.0 BT:-1.7	10 (i.p.)	+ (CFS)
Example 7-20 	3 (i.p.)	LLR:0.8 FBP:0.8 BT:-0.4	1 (i.p.)	- (CFS)
			3 (i.p.)	+ (CFS)
	10 (i.p.)	LLR:1.6 FBP:1.8 BT:-1.2	10 (i.p.)	+ (CFS)
TZB-41044 	10 (i.p.)	LLR:0.4 FBP:0.2 BT:0.1	30 (i.p.)	- (CFS)
	30 (i.p.)	LLR:0.2 FBP:1.4 BT:-0.9		

BT*1: Body Temperature, CFS*2: Conditioned Fear Stress